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# Roles of Increase Fatty Acid Utilization in the Pathological Pathway of Heart Failure in Diabetes

**Wenjia Lyu**

Guangzhou Huamei International School, #23 Huamei Road, Tianhe District, Guangdong, China, 510520

jessicalvgiahmis@gmail.com

**Abstract.** This paper reviews the molecular mechanism that led diabetic patients to its major complication heart failure. While AGEs, RAAS, impaired Ca2+ handling, and ER stress also contribute to the progress of diabetic cardiomyopathy, this review emphasizes on the effect of increasing fatty acid (FA) uptake and utilization since it interconnects with other crucial causes of diabetic cardiomyopathy such as lipotoxicity, mitochondrial dysfunction, and myocardial apoptosis. The review started with the root of increasing myocardial FA metabolism, which is the overactivation of a transcription factor called peroxisome proliferator-activated receptor α (PPARα). Then, the paper detailedly reviews the molecular mechanism of how increasing FA oxidation and impaired glucose oxidation leads to lipid accumulation, apoptosis, and cardiac inefficiency, which ultimately causes contractile dysfunction, left ventricular hypertrophy, and heart failure.

**Keywords:** fatty acid utilization, diabetes, heart failure, PPARα, lipoapoptosis, cardiac inefficiency

## 1. Introduction

Diabetes is a condition in which people have high blood sugar level. This suggests that diabetic patients have a lower ability to metabolize glucose. Besides increasing blood glucose levels, statistical analysis of 11 healthy patients and 11 T1DM patients had shown an elevated fatty acid (FA) concentration in the blood of T1DM, which was three times higher than the control patients ($0.60 \pm 0.24$ μmol/ml vs. $0.19 \pm 0.07$ μmol/ml, $p < 0.0001$) [1]. In addition, the T1DM patients' heart also showed an increase in uptake and oxidation of fatty acid, supported by higher myocardial oxygen consumption ($MVO_2$, $6.64 \pm 2.21$ μmol/g/min vs. $4.51 \pm 1.39$ μmol/g/min, $p < 0.007$) and overall myocardial fatty acid utilization ($213 \pm 135$ nmol/g/min vs. $57 \pm 28$ nmol/g/min, $p = 0.0004$) [1]. These symptoms are associated with increasing the risk of heart failure. Heart failure is the leading cause of death in diabetic patients, a condition in which the heart is too weak to pump blood around the body [2][3]. In fact, according to the data from the Get With the Guidelines–Heart Failure registry, 44% of all heart failure hospitalization has diabetes [4]. 12% of diabetic patients in the Reykjavik population study have heart failure, rising to 22% in diabetic patients above 64 years of age [5]. While most studies focus on the influence of glucose-lowering agents or antidiabetic agents on heart failure, this review emphasizes on the molecular mechanisms of elevated blood FA uptake and oxidation that progress diabetic cardiomyopathy by analyzing the experimental results that measure the various protein channels and enzymes that facilitate FA uptake and oxidation, lipid accumulation, level of

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ceramide, and myocardial apoptosis in rats and proposed potential molecular mechanisms based on these data.

## 2. Structural and functional changes of heart in diabetic patient

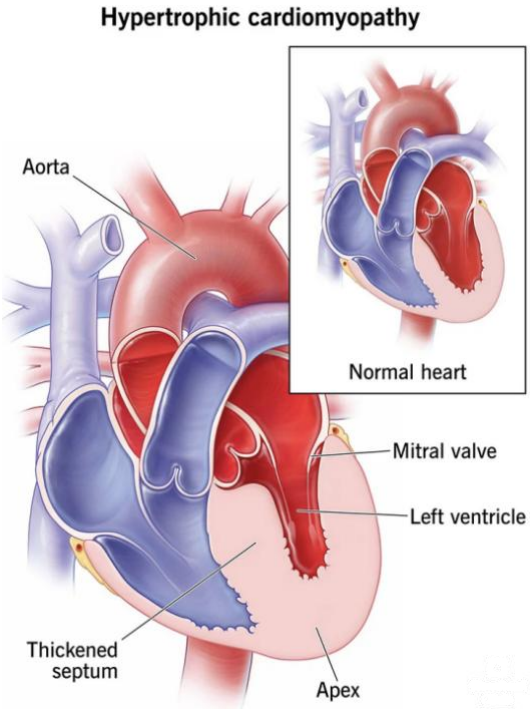


**Figure 1.** Hypertrophic cardiomyopathy [6].

The most significant change in the heart of diabetic patients is cardiac hypertrophy, defined as "abnormal thickening of the heart muscle" by Nature [7]. The evidence had been shown in Richard B. Devereux's study: the LV mass of diabetic women is 9% to 14% greater than women who can successfully metabolize glucose, suggesting an increase in LV muscle mass (155 ± 40 g vs. 138 ± 32 g; $P < 0.0001$) [8]. The mean septal is also greater in diabetic women (0.95 ± 0.13 cm vs. 0.87 ± 0.11; $P < 0.0001$) [8]. Similarly, the men also produced a similar result, with 6% to 12% greater LV mass in diabetic men [8]. The thickening of the septum muscle, if develop severely, can block the pathway from the LV to the aorta. The thickening of LV muscle will reduce the blood it can hold, decreasing heart efficiency in pumping blood (as shown Figure 1) [6].

## 3. Mechanism of increasing utilization of fatty acid (FA)

Although, normally, the heart relied on FA to support its 60~70% of energy demand, a greater reliance on FA reduces the heart efficiency (as $MVO_2$ increases), which leads to contractile dysfunction [9][10]. The overactivation of PPARα in diabetic patients is one explanation for this increase [11]. PPARα is a transcription factor that activated by attaching to ligands including FA [11]. Hence, greater FA concentration in the circulation will result in more PPARα activation in diabetic patients. When FA from the blood or adipose tissue binds to PPAR, activated PPAR binds with the retinoid X receptor (RXR) and PPAR-coactivator 1 (PGC-1) to form a complex that can bind to the promoter called PPAR response elements (PPRE) (Figure 2) [10]. Because it encodes many fatty acid transporters, enzymes involved in fatty acid oxidation, and pyruvate dehydrogenase kinase 4 (PDK4), which inactivates pyruvate dehydrogenase, an enzyme that catalyzes pyruvate into acetyl-CoA [10], the target gene influences FA and glucose utilization. Combined, overactivation of PPARα due to elevated blood FA levels in diabetic patients will facilitate FA oxidation since it increases the expression of proteins that increase the amount of FA transporters (CD36/FAT, FABP, FATP, FACS) and catalyst of mitochondrial

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FA oxidation (MCD, MCAD, LCAD, VLCAD), but reduce glucose oxidation by expressing PDK4 [10]. This mechanism was supported by the observed increase of expression of CD36/FAT, FABP, and PDK4 in obese rats, which will be presented in the Evidence section.

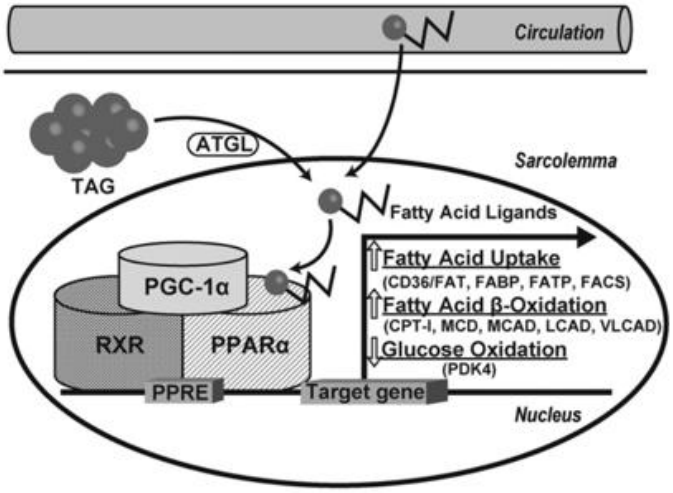


**Fig. 2.** Alterations in transcriptional regulation of fatty acid enzymes in heart failure associated with obesity and diabetes. The peroxisome proliferator activated receptor (PPAR) family of transcription factors forms a heterodimer complex with the retinoid X receptor (RXR). PPAR-γ coactivator 1α (PGC-1α) coactivates and enhances PPARα-mediated transcription. The complex binds to PPAR response elements (PPRE) which is located in the promoter region of target genes. These target genes include enzymes involved in fatty acid uptake, fatty acid β-oxidation, and control of glucose oxidation. In obese or diabetic hearts, the PPARα-PGC1 pathways are upregulated by increased PPAR ligands derived from circulating fatty acids and/or intracellular triacylglycerol catabolism via adipose triglyceride lipase (ATGL). PPAR, peroxisome proliferator activated receptor; RXR, retinoid X receptor; PGC-1α, PPAR-γ coactivator 1α; PPRE, PPAR response elements; TAG, triacylglycerol; ATGL, adipose triglyceride lipase; CD36/FAT, fatty acid translocase; FABP, fatty acid binding protein; FATP, fatty acid transport protein; FACS, fatty acyl CoA synthase; CPT, carnitine palmitoyl transferase; MCD, malonyl CoA decarboxylase; LCAD, long-chain acyl CoA dehydrogenase; MCAD, medium-chain acyl CoA dehydrogenase; VLCAD, very long-chain acyl CoA dehydrogenase; PDK4, pyruvate dehydrogenase kinase 4.

**Figure 2.** Mechanism of increase fatty acid uptake and concentration in myocytes in diabetic patients. CD36/FAT: fatty acid translocase; FATP: fatty acid transport protein; FACS: fatty acyl CoA synthase[12].

## 4. The mechanisms of increasing fa uptake and oxidation induces heart failure

There are two ways that increase FA uptake and oxidation can deteriorate heart functioning. One is by inducing myocytic apoptosis; another way is by inducing cardiac inefficiency.

### *4.1. Apoptosis*

Myocytic apoptosis is caused by toxic lipid accumulation in myocytes. This lipid accumulation, according to Finck et al., was caused by the intake of FA was higher than the rate of consumption [12]. Excessive saturated fatty acid in the heart causes increased synthesis of ceramide since ceramide consists of a sphingosine backbone and fatty acid, so as fatty acid substrate increases, ceramide, the product, will also increase [13]. Ceramide can induce myocardial apoptosis because it can form channels in the mitochondrial membrane that increases the its permeability [14]. Hence, small proteins and cytochrome c in the mitochondria might have leaked out to the cytoplasm (the evidence for the increase in both ceramide and cytochrome c in lipid overload mice is presented in the Evidence section). Cytochrome c then activate Apaf-1 and caspase 9, which form apoptosome that activates caspase 3 [14]. Finally, caspase 3 will degrade proteins and actin filaments, which eventually lead to

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cell death [14]. Therefore, increasing FA uptake and oxidation can lead to lipoapoptosis by increasing the level of ceramide. However, Siskind et al. asserted that the ceramide channel on the mitochondrial membrane didn't trigger cytochrome c secretion or release because cytochrome c can move freely and is reversible [15]. Therefore, although ceramide is known to be involved in regulating apoptosis, the specific molecular mechanism of how ceramide progress apoptosis requires further study. According to Baraka et al., apoptosis can lead to heart failure since it causes "loss of contractile tissue, compensatory hypertrophy, and reparative fibrosis", linking elevated FA concentration to the progression of heart failure. But the exact mechanism of how apoptosis progresses heart failure needs to be further identified [16].

### *4.2. Cardiac inefficiency*

Increased FA oxidation can decrease cardiac inefficiency not only because FA yields less ATP per oxygen atom (2.33 in palmitate vs. 2.58 in glucose) but also due to increased mitochondrial uncoupling protein 3 (UCP3) levels [17][18]. According to Cole et al., FA is the "intrinsic activator" of UCP3 [18]. As a result, elevated FA levels in diabetic patients will also have overactivated UCP3, as evidenced by a 20% increase in UCP3 level in high-fat-fed mice compared to rats fed a normal diet [18]. UCP3 can embed in the mitochondrial membrane and allows protons can move back to the mitochondrial matrix. Hence, the generation of ATP decreased, reducing the work done by the myocyte while increasing oxygen consumption due to fatty acid oxidation. Theoretically, cardiac hypertrophy can develop since myocytes have to contract harder, hence grow larger, to compensate for the decreasing cardiac efficiency. However, the exact mechanism of how cardiac inefficiency progresses to left ventricular hypertrophy or heart failure requires further study. Many studies have merely suggested that myocardial FA metabolism plays a role as an independent factor or is correlated with cardiac hypertrophy [12].

## 5. Evidence

Finck et al. mimicked the overactivation of PPARα due to increasing blood FA concentration in diabetic patients by producing transgenic mice (MHC-PPAR) that overexpressed PPARα. Compared to non-transgenic (NTG) mice. All MHC-PPAR had greater FATP1, FACS1, and CD36 (as shown in Table 1) [11]. When the same group of mice had been treated with Wy-14, 643 chow, a synthetic PPARα activator, both NTG and MHC-PPAR mice showed an increase in the three proteins (as shown in Table 1) [11]. This showed the essential role of transcription factor PPARα in regulating the expression of proteins that involve in FA uptake. Therefore, it's reasonable that overactivation of PPARα due to increasing FA binding in diabetic patients can cause increase FA uptake in their hearts.

**Table 1.** Comparison of the amount of FATP1, FACS1, CD36 in non-transgenic (NTG) and transgenic (MHC-PPAR) mice before and after the administration of Wy-14, 643 chow [11].

| **404-3 mice** | **Control chow** | | **Wy-14, 643 chow (0.1%)** | |
|---|---|---|---|---|
| *Gene* | NTG | MHC-PPAR | NTG | MHC-PPAR |
| FATP1 | 1.0±0.30^ | 1.0±0.09^ | 1.6±0.42^ | 1.9±0.24^ |
| FACS1 | 1.0±0.20^ | 1.3±0.18^ | 1.5±0.15^ | 3.2±0.40^ |
| CD36 | 1.0±0.21^ | 1.5±0.24^ | 0.9±0.23^ | 2.7±0.13^ |

(FATP1: fatty acid transport protein-1; FACS1:fatty acid CoA synthase-1; CD36: fatty acid translocase. ^Significant difference is P<0.05 [11]).

Furthermore, GLUT4 arbitrary unit was lower in MHR-PPAR compared to NTG mice, whereas PDK4 was higher after the PPARα gene had been activated by Wy-14, 643 chow (as shown in Figure 3) [11]. Hence, glucose oxidation will be lower in diabetic patients' hearts after PPARα overactivation is reliable. Ultimately, Finck's MHC-PPAR mice showed myocardial palmitate oxidation (294 ± 44 vs. 179 ± 9 nmol/min/g dry weight; $P < 0.05$) and impaired glucose oxidation (302 ± 150 vs. 824 ± 72 nmol/min/g dry weight; $P < 0.05$) [11]. Moreover, Finck also observed significant lipid accumulation in MHC-PPAR using oil red O staining pattern (as shown in Figure 4) and greater LV internal diameter at diastole (3.3±0.04 vs. 3.6±0.04; $P < 0.05$) [11]. But none of the mice had apoptosis [11]. This

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suggests that the observed hypertrophy might be due to energetic inefficiency or other unknown causes rather than apoptosis.

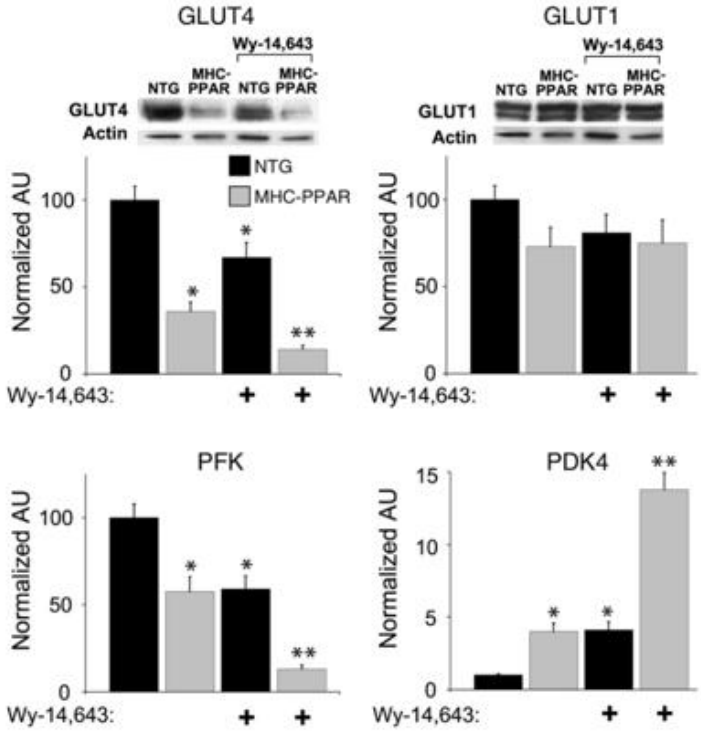


**Figure 3.** Arbitrary units of GLUT4 and PDK4 in MHF-PPAR mice [11].

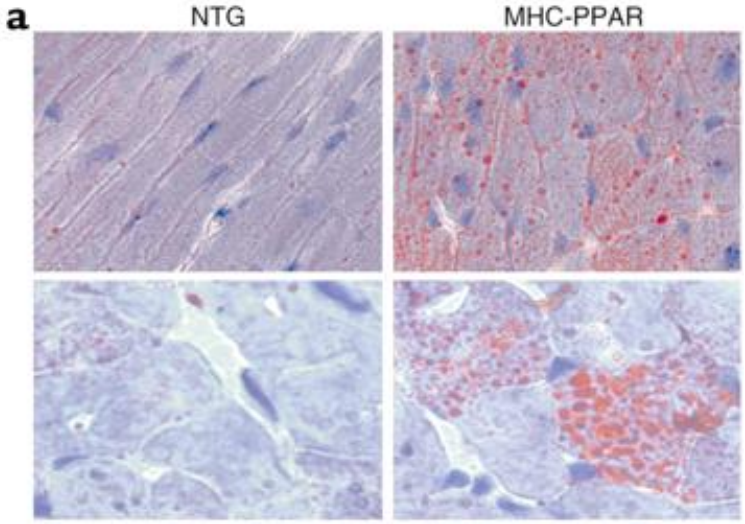


**Figure 4.** Red droplets indicate neutral lipid staining in frozen tissue section [11].

By contrast, Chui et al. noted that the observed ventricular hypertrophy in the mice of his team, which exhibited intracellular lipid accumulation in myocytes by overexpressing long-chain acyl- CoA synthetase (ACS), was simply lipid accumulation since other signification of hypertrophy such as phospholamban, α-skeletal actin, and SERCA hadn't increase [19]. The ceramide level, however, had been found 3.3 folds increase in transgenic mice, as well as the cytochrome c arbitrary units (as shown in Figure 5) [19]. Therefore, Chui et al. concluded that apoptosis accounted for the resulting

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left-ventricular dysfunction instead of hypertrophy.

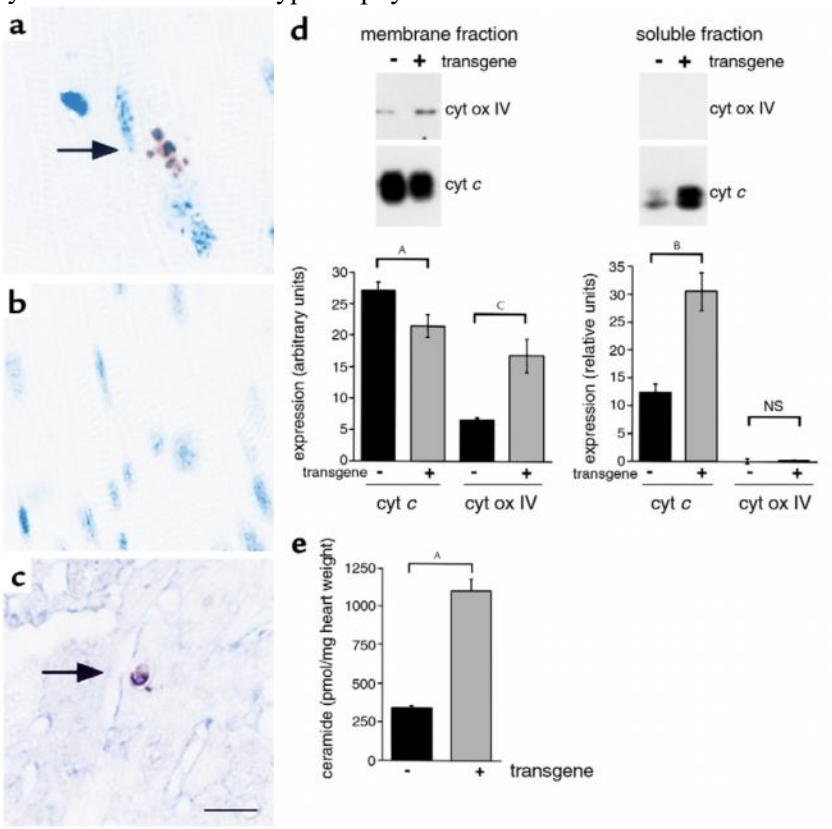


**Figure 5.** a and c are slices of ventricle from a MHC-ACS mice. The arrow represented the apoptosis. The blue staining was myocyte cytoplasm. d measured the expression of cytochrome c in MHC-ACS mice. $^{A}P=0.06$, $^{B}P=0.01$, $^{C}P<0.01$. e measured the ceramide level in the heart tissue from 19-day-old MHC-ACE mice using the diacyglycerol kinase assay. [19]).

## 6. Discussion

PPARα over-activation due to elevated blood FA level in diabetic patients increases myocardial FA uptake and oxidation and lipid accumulation. Since ceramide level will also increase and form channels in the mitochondrial membrane, cytochrome c will leak out from the mitochondria to the cytoplasm, which activate the apoptosis pathway of myocytes. However, whether cytochrome c can penetrate the channel is still controversial, and the mechanism of how apoptosis progresses to heart failure requires further study. But Chui et al.'s mice experiment on over-express PPARα observed the link between fatty acid level, ceramide level, cytochrome c level, apoptosis, left ventricular dysfunction, and premature death. Another effect of increasing myocardial FA metabolism is cardiac inefficiency. The increasing mitochondrial uncoupling protein 3 due to elevated fatty acid levels accounts for the inefficiency. But the causation of cardiac inefficiency and the development of left ventricular hypertrophy require further study to clarify whether cardiac inefficiency is the cause that led to hypertrophy or vice versa.

## 7. Conclusion

Overall, this paper reviews the mechanisms of increasing fatty acid concentration in diabetic patients that lead to HF through lipoapoptosis and cardiac inefficiency. Besides, the review opens new ways of preventing diabetic patients from HF such as through PPARα antagonist and UCP3. However, the lack

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of accessibility to laboratory limited this review to investigate the effect of ceramide channel on cytochrome c and the molecular mechanism of how apoptosis progress heart failure. Since the published experiments about these two areas obtained inconsistent conclusions, to clarify the molecular mechanisms, further studies are required.

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